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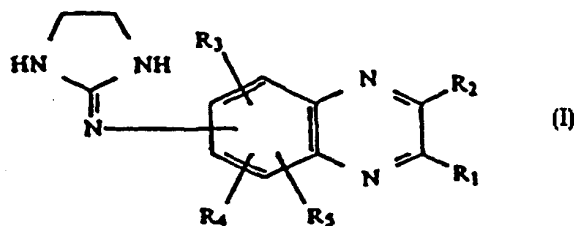
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<p>(21) International Application Number: PCT/US94/10569 (22) International Filing Date: 19 September 1994 (19.09.94) (30) Priority Data: 08/135,716 13 October 1993 (13.10.93) US (71) Applicant: ALLERGAN, INC. [US/US]; 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US). (72) Inventors: BURKE, James, A.; 670 West Third Street, Tustin, CA 92680 (US). GARST, Michael, E.; 2433 Vista Hogar, Newport Beach, CA 92660 (US). WHEELER, Larry, A.; 18 Valley View, Irvine, CA 92715 (US). (74) Agents: BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).</p>		<p>(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report. With amended claims and statement.</p>

(54) Title: METHODS FOR USING (2-IMIDAZOLIN-2-YLAMINO) QUINOXALINE DERIVATIVES

(57) Abstract

A method of treating a mammal comprises administering to a mammal an effective amount to provide a desired therapeutic effect in the mammal of a compound selected from the group consisting of those having formula (I), and pharmaceutically acceptable acid addition salts thereof and mixtures thereof, wherein R<sub>1</sub> and R<sub>2</sub> each is selected from the group consisting of alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms, the 2-imidazolin-2-ylamino group may be in any of the 5-, 6-, 7- or 8- positions of the quinoxaline nucleus, and R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> each is located in one of the remaining 5-, 6-, 7- or 8- positions

of the quinoxaline nucleus and is independently selected from the group consisting of Cl, Br, H and alkyl radicals containing 1 to 3 carbon atoms. Such compounds, when administered to a mammal, provide desired therapeutic effects, such as reduction in peripheral pain, anesthetization of the central nervous system, constriction of one or more blood vessels, reduction in or prevention of at least one effect of ischemia, decongestion of one or more nasal passages, reduction of at least one effect of an inflammatory disorder, increase in renal fluid flow, and alteration in the rate of fluid transport in the gastrointestinal tract.



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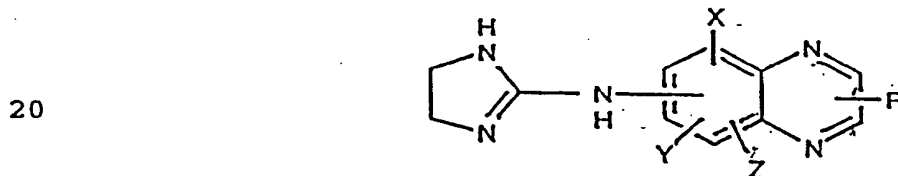
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METHODS FOR USING (2-IMIDAZOLIN-2-YLAMINO)  
QUINOXALINE DERIVATIVES

Background of the Invention

The present invention relates to certain derivatives of quinoxaline. More particularly, the invention relates to methods of using such derivatives as therapeutic agents, for example, to effect reduction in peripheral  
5 pain, to anesthetize the central nervous system, to constrict one or more blood vessels, to treat ischemia, to decongest one or more nasal passages, and to effect reduction of one or more effects of an inflammatory disorder to increase renal fluid flow and to effect an  
10 alteration in the rate of fluid transport in the gastrointestinal tract.

Various quinoxaline derivatives have been suggested as therapeutic agents. For example, Danielewicz, et al U.S. Patent 3,890,319 discloses compounds as regulators of  
15 the cardiovascular system and, in particular, in the treatment of hypertension, which have the following formula:



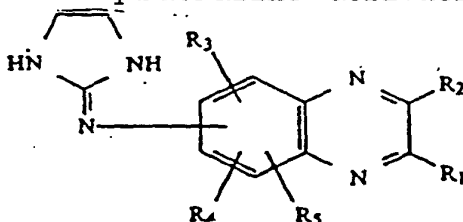
where the 2-imidazolin-2-ylamino group may be in any of the 5-, 6-, 7- or 8- position of the quinoxaline nucleus;  
25 X, Y and Z may be in any of the remaining 5-, 6-, 7- or 8- positions and may be selected from hydrogen, halogen, lower alkyl, lower alkoxy or trifluoromethyl; and R is an optional substituent in either the 2- or 3- position of the quinoxaline nucleus and may be hydrogen, lower alkyl  
30 or lower alkoxy. Gluchowski U.S. Patent 5,021,416 discloses the use of similar quinoxaline derivatives to reduce or maintain the intraocular pressure in a mammalian

eye. There is no suggestion in either of these patents that such compounds are useful in reducing peripheral pain, as central nervous system anesthetics, as vaso-constricting agents, to treat ischemia, as a nasal passage  
5 decongestant, to treat inflammatory disorders, to increase renal fluid flow or to alter the rate of fluid flow in the gastrointestinal tract.

#### Summary of the Invention

New methods for treating mammals, preferably human  
10 beings, to provide a desired therapeutic effect have been discovered. By administering an effective amount of one or more of certain compounds to a mammal, a desired therapeutic effect is provided in the mammal. Such desired therapeutic effects include reduction in  
15 peripheral pain, anesthetization of the central nervous system, constriction of one or more blood vessels, reduction in or prevention of at least one effect of ischemia, decongestion of one or more nasal passages, reduction in at least one effect of an inflammatory  
20 disorder, increase in renal fluid flow, and alteration, preferably decrease, in the rate of fluid transport in the gastrointestinal tract.

The quinoxaline derivatives useful in the present invention are those quinoxaline derivatives having the  
25 formula



30 , pharmaceutically acceptable acid addition salts thereof and mixtures thereof.  $R_1$  and  $R_2$  each is independently selected from the group consisting of H, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms.  $R_2$  is preferably a methyl  
35 radical. The 2-imidazolin-2-ylamino group may be in any

of the 5-, 6-, 7- or 8- positions, preferably in the 6-position, of the quinoxaline nucleus.  $R_3$ ,  $R_4$  and  $R_5$  each is located in one of the remaining 5-, 6-, 7- or 8-positions of the quinoxaline nucleus and is independently  
5 selected from the group consisting of Cl, Br, H and alkyl radicals containing 1 to 3 carbon atoms.  $R_3$  is preferably in the 5- position of the quinoxaline nucleus, and  $R_4$  and  $R_5$  are preferably both H. In a particularly useful embodiment  $R_3$  is Br.

10 In one embodiment,  $R_1$  is H and  $R_2$  is selected from alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms.  $R_3$  may advantageously be in the 5-position of the quinoxaline nucleus and be selected from H and alkyl radicals  
15 containing 1 to 3 carbon atoms.

All stereoisomers, tautomers and mixtures thereof which comply with the constraints of one or more of the presently useful compounds are included within the scope of the present invention.

20 Pharmaceutically acceptable acid addition salts of the compounds of the invention are those formed from acids which form non-toxic addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, sulfate, or  
25 bisulfate, phosphate or acid phosphate, acetate, maleate, fumarate, oxalate, lactate, tartrate, citrate, gluconate, saccharate and p-toluene sulphonate salts.

#### Detailed Description of the Invention

The present invention involves methods for treating  
30 mammals to provide one or more desired therapeutic effects in the mammal. The present methods comprise administering an effective amount to provide the desired therapeutic effect or effects in a mammal of at least one compound, as described herein, to the mammal. Among the desired  
35 therapeutic effects are reduction in peripheral pain,

anesthetization of the central nervous system, constriction of one or more blood vessels, reduction in or prevention of at least one effect of ischemia, decongestion of one or more nasal passages, reduction in  
5 at least one effect of an inflammatory disorder, for example, such disorders characterized by progressive joint and/or tissue deterioration, increase in renal fluid flow, and alternation, preferably decrease, in the rate of fluid transport in the gastrointestinal tract. Thus, for  
10 example, the presently useful compounds may be effective as one or more of the following: a peripheral pain killing agent, a general anesthetic, a vaso-constricting agent, an agent for the treatment of ischemia, a nasal decongestant, an anti-inflammatory agent, a medication for use in the  
15 treatment or management of kidney disease, and an anti-diarrhea agent. One important feature of many of the present methods is that the desired therapeutic effect is achieved with reduced side effects, in particular with reduced effects on the blood pressure of the mammal to  
20 which the presently useful compound or compounds are administered.

Any suitable method of administering the presently useful compound or compounds to the mammal to be treated may be used. The particular method of administration  
25 chosen is preferably one which allows the presently useful compound or compounds to have the desired therapeutic effect in an effective manner, e.g., low medication concentration and low incidence of side effects. In many applications, the presently useful compound or compounds  
30 are administered to a mammal in a manner substantially similar to that used to administer alpha agonists, in particular alpha 2 agonists, to obtain the same or similar therapeutic effect or effects.

Administration of the presently useful compounds for  
35 use in the methods of this invention can include, but are

not limited to, oral, parenteral, topical, intra-articular and other modes of systemic administration. The compounds are administered in a therapeutically effective amount either alone or in combination with a suitable  
5 pharmaceutically acceptable carrier or excipient.

Depending on the intended mode of administration, the presently useful compound or compounds may be incorporated in any pharmaceutically acceptable dosage form, such as for example, tablets, suppositories, pills, capsules,  
10 powders, liquids, suspensions, emulsions, aerosols or the like, preferably in unit dosage forms suitable for single administration of precise dosages, or sustained release dosage forms for continuous controlled administration. Preferably, the dosage form will include a  
15 pharmaceutically acceptable excipient and the presently useful compound or compounds and, in addition, may contain other medicinal agents, pharmaceutical agents, carriers, adjuncts, etc.

For solid dosage forms, non-toxic solid carriers  
20 include, but are not limited to, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, the polyalkylene glycols, talcum, cellulose, glucose, sucrose and magnesium carbonate. An example of a solid dosage form for carrying out the invention is a  
25 suppository containing propylene glycol as the carrier. Liquid pharmaceutically administrable dosage forms can, for example, comprise a solution or suspension of one or more of the presently useful compounds and optional pharmaceutical adjuncts in a carrier, such as for  
30 example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying  
35 agents, pH buffering agents and the like. Typical

examples of such auxiliary agents are sodium acetate, sorbitan monolaurate, triethanolamine, sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, 16th Edition, 1980. The composition of the formulation to be administered, in any event, contains a quantity of one or more of the presently useful compounds in an amount effective to provide the desired therapeutic effect.

Parenteral administration is generally characterized by injection, either subcutaneously, intramuscularly or intravenously. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol and the like. In addition, if desired, the injectable pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like.

The amount of the presently useful compound or compounds administered is, of course, dependent on the therapeutic effect or effects desired, on the specific mammal being treated, on the severity and nature of the mammal's condition, on the manner of administration, on the potency and pharmacodynamics of the particular compound or compounds employed, and on the judgement of the prescribing physician. The therapeutically effective dosage of the presently useful compound or compounds is preferably in the range of about 0.5 or about 1 to about 100 mg/kg/day.

The presently useful compounds are as described



above. The presently useful compounds may be prepared in accordance with the procedures described in Danielewicz, et al U.S. Patent 3,890,319 for the production of the quinoxaline derivatives therein. This patent is hereby  
5 incorporated in its entirety by reference herein.

Briefly, the presently useful 2-imidazolin-2-ylamino quinoxaline derivatives may be prepared by (1) reaction of the appropriate amino-quinoxaline with thiophosgene to form the corresponding isothiocyanate; and (2) reacting  
10 this isothiocyanate with excess ethylene diamine to form the corresponding beta-aminoethyl-thioureidoquinoxaline, which is then cyclized to the corresponding derivative. Alternately, such derivatives can be prepared by (1) reacting the corresponding aminoquinoxaline with benzoyl  
15 isothiocyanate to form the corresponding N-benzoyl thioureido compound, followed by hydrolysis to the thioureido compound, or reaction of the aminoquinoxaline with ammonium thiocyanate to form the thioureido compound directly; (2) methylation to form the S-methyl derivative  
20 of the thioureido compound; and (3) reaction with ethylene diamine to form the derivative.

For derivatives in which the  $R_3$  group is to be alkyl, the corresponding bromo derivative can be produced and than subjected to an alkylation reaction in which the  
25 bromo group is replaced by the desired alkyl group. This alkylation reaction is conveniently conducted using an alkylation agent, such as an alkyl metallic component, e.g., alkyl stannane, in the presence of a platinum group metal-containing catalyst. For example, if it is desired  
30 to substitute a methyl group for the bromo group, the bromo derivative is contacted with tetramethyl tin in the presence of a palladium-containing catalyst, e.g.,  $(Ph_3P)_2PdCl_2$ , at conditions to effect the desired alkylation or substitution.

35 The following non-limiting examples illustrate

certain aspects of the present invention.

EXAMPLE 1

Preparation of 6-(2-imidazolin-2-ylamino) quinoxaline  
1,2,4-Triaminobenzene dihydrochloride

5 To a suspension of 4-nitrophenylenediamine (Aldrich,  
10 g, 65.3 mmol) in absolute ethanol (240 ml) was added  
600 mg of 10% by weight palladium on charcoal catalyst.  
The container including the suspension was evacuated and  
filled with hydrogen three times and the suspension was  
10 hydrogenated at 18 psi until hydrogen uptake ceased. The  
reaction was slightly exothermic and one refill of  
hydrogen was required. The resulting light yellow  
solution, which darkens rapidly on contact with air, was  
filtered and concentrated to about 150 ml. Concentrated  
15 hydrochloric acid (12 ml) was added and the solid formed  
was filtered off. After drying in vacuo overnight, 12 g  
(a yield of 93%) of purple solid was obtained, m.p. 224-5°  
C. Using various analytical procedures, this solid was  
determined to be 1,2,4-triaminobenzene dihydrochloride.

20 6-Aminoquinoxaline

Glyoxal sodium bisulfite adduct (Aldrich, 14.3g, 50  
mmol) was added in small portions to a solution of 1,2,4-  
triaminobenzene dihydrochloride (9.8 g, 50 mmol) in 200 ml  
of 10% by weight sodium carbonate in water. The reaction  
25 mixture was heated to 100° C for two hours and then cooled  
to 0° C. The crystals formed were filtered off and dried  
in vacuo to give a crude yield of 7.06 g (a yield of 97%)  
of brown crystals. Recrystallization from benzene gave  
6.32 g (a yield of 87%) yellow crystals, m.p. 157-8° C.  
30 Using various analytical procedures, these yellow crystals  
were determined to be 6-aminoquinoxaline.

6-(2-imidazolin-2-ylamino) quinoxaline

6-Aminoquinoxaline (1.00 g, 7.5 mmol) was suspended  
in 15 ml of water and thiophosgene (0.64 ml, 8.4 mmol) was  
35 added in small portions with vigorous stirring. The

starting material dissolved and after 2 hours the red color of the solution was discharged. The solid formed was removed by vacuum filtration and washed with water. The crude isothiocyanate thus obtained was used without  
5 further purification. A solution of the isothiocyanate in benzene (70 ml) was contacted with ethylenediamine (Aldrich, 2.71 g, 45 mmol) in 10 ml of benzene at 25°C for 30 minutes. After stirring for an additional 30 minutes, the supernatant was poured off. The crude thiourea thus  
10 obtained was washed three (3) times with 10 ml dry ether and used directly for the next step. The crude product was dissolved in 30 ml of dry methanol and the dark green solution was heated at reflux for 15 hours until hydrogen sulfide gas was no longer evolved. The mixture was cooled  
15 to room temperature and concentrated in vacuo. The resulting dark green solid was chromatographed ( $\text{SiO}_2$ , 90/10  $\text{CHCl}_3/\text{CH}_3\text{OH}$  saturated with  $\text{NH}_3$  (g)) to yield a dark green solid which was recrystallized from  $\text{CH}_3\text{OH}$  to yield 1.11 g of the title compound as a light green crystalline  
20 solid, mp 232-234° C. The yield was 70%. The compound was characterized by  $^1\text{H}$  and  $^{13}\text{CNMR}$ , IR and mass spectral analysis.

#### EXAMPLE 2

Preparation of 5-bromo-6-(2-imidazolin-2-ylamino)  
25 quinoxaline

##### 6-Amino-5-bromoquinoxaline hydrobromide

6-Aminoquinoxaline (2.08 g, 14.4 mmol) was dissolved in 11.5 ml glacial acetic acid. The solution was cooled in water while a solution of bromine (0.74 ml, 2.3g, 14.4  
30 mmol) in 1.5 ml glacial acetic acid was added slowly over 15 min. After stirring for an additional 30 min, the orange red solid formed was filtered off and washed thoroughly with dry ether. The solid was dried in vacuo overnight to yield 4.44 g crude product (a yield of 100%).  
35 The compound, 6-amino-5-bromoquinoxaline hydrobromide, had

no definite melting point. A phase change (from fine powder to red crystals) was noticed at about 220° C. Decomposition was observed at about 245° C. It was used directly for the next step.

5 6-Amino-5-Bromoquinoxaline

The crude 6-amino-5-bromoquinoxaline from above was dissolved in water and saturated sodium bisulfite solution was added until the resulting solution tested negative with starch-iodide paper. The solution was then basified  
10 with 2N sodium hydroxide and extracted thoroughly with ethyl acetate. The organic extract was dried over magnesium sulfate and concentrated under reduced pressure to give the free base. The crude product was recrystallized from boiling benzene to give yellow  
15 crystals, m.p. 155-6° C. Using various analytical procedures, the yellow crystals were determined to be 6-amino-5-bromoquinoxaline. The yield was 82%.

5-Bromo-6-isothiocyantoquinoxaline

20 The crude hydrobromide product previously noted (4.27g, 14.0 mmol) was dissolved in 60 ml of water and thiophosgene (Aldrich, 1.28 ml, 16.8 mmol) was added in small portions with vigorous stirring. After 2 hours, the red color of the solution was discharged. The solid  
25 formed was filtered off and washed thoroughly with water. After drying in vacuo at 25° C, 3.38 g (a yield of 90%) of brick red crystals was obtained, m.p. 157-8° C. A portion of this material was further purified by column chromatography to give white crystals, m.p. 157-8° C.  
30 Using various analytical procedures, these crystals were determined to be 5-bromo-6-isothiocyantoquinoxaline.

5-Bromo-6(-N-(2-aminoethyl)thioureido)quinoxaline

A solution of the isothiocyanate (3.25 g, 12.2 mmol) in 145 ml benzene was added to a solution of  
35 ethylenediamine (Aldrich, 5.43 g, 90.0 mmol) in 18 ml

benzene at 25° C over 2 hours. After stirring for a further 30 min., the supernatant was poured off. The oil which remained was washed by swirling with dry ether three times and used directly for the next step.

- 5 A portion of this product was further purified by column chromatography (SiO<sub>2</sub>, CHCl<sub>3</sub>) for characterization. A white solid was recovered which decomposed at 175° C with gas evolution (puffing). This white solid was determined to be 5-bromo-6(-N-2-  
10 (aminoethyl)thioureido) quinoxaline.

5-Bromo-6-(2-imidazolin-2-ylamino)quinoxaline

The crude product from above was dissolved in 100 ml dry methanol and the brown solution was refluxed for 19 hours until hydrogen sulfide gas was no longer evolved.

- 15 The mixture was cooled to room temperature and concentrated to about 50 ml. The yellow solid was filtered off and dried in vacuo; weight 2.52 g (a yield of 70%), mp 242-4° C.

- As the crude product was insoluble in most common  
20 organic solvents, initial purification was achieved by an acid-base extraction procedure. 23 g of the crude product was dissolved in 100 ml 0.5N hydrochloric acid. The turbid yellow solution was filtered to give a clear orange yellow solution which was extracted twice with ethyl  
25 acetate (2 X 10 ml). The aqueous phase was cooled to 0° C and basified with 6N sodium hydroxide, keeping the temperature of the solution below 15° C at all times. The yellow solid which precipitated was filtered off and washed thoroughly with water until the washings were  
30 neutral to pH paper. The solid was dried overnight in vacuo to give 1.97 g yellow solid, m.p. 249-50° C. The recovery was about 88%.

- Further purification was achieved by recrystallization as described below. The partially  
35 purified product from above was dissolved in N, N-

dimethylformamide (about 17 ml/g) at 100° C with vigorous stirring. The solution was filtered hot and set aside to cool overnight. The bright yellow crystals were collected by filtration, m.p. 252-3° C. Recovery was from 65-77%.

- 5 Using various analytical procedures, the bright yellow solid was determined to be 5-bromo-6-(2-imidazolin-2-ylamino) quinoxaline.

#### EXAMPLE 3

Preparation of 5-Methyl-6-(2-imidazolin-2-ylamino)quinoxaline

- A sealable reaction tube was charged with 5-bromo-6-(2-imidazolin-2-ylamino) quinoxaline (104 mg., 0.36 mmol) (prepared as noted above), tetramethyl tin (214 mg., 1.2 mmol) and (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> (10 mg) and dry dimethylformamide (2 ml) in a reaction tube. The reaction mixture was purged with dry nitrogen gas. The tube was sealed and heated to 145° C for 6 hours. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The dark brown residue was chromatographed (SiO<sub>2</sub>; 5/1 CHCl<sub>3</sub>/CH<sub>3</sub>OH saturated with NH<sub>3</sub> (g)) to yield 46.5 mg (53%) of the title compound as a light yellow solid. An analytical sample was prepared by recrystallization from CHCl<sub>3</sub>/CH<sub>3</sub>OH and had a melting point of 183-186°C. The title compound was characterized by <sup>1</sup>H and <sup>13</sup>CNMR, IR and mass spectral analysis.

#### EXAMPLE 4

Preparation of 2-Methyl-5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline

##### 2-Methyl-6-nitroquinoxaline

- A solution of pyruvic aldehyde (Aldrich, 40% solution in H<sub>2</sub>O, 11.8 g, 65.3 mmol) was added dropwise to a solution of 4-nitro-1,2-phenylenediamine (Aldrich, 10g, 65.3 mmol) in 150 ml of H<sub>2</sub>O. The reaction mixture was heated to 80° C for four hours. The reaction was cooled to room temperature, diluted with water and extracted with

CHCl<sub>3</sub>. The organic extracts were dried over MgSO<sub>4</sub> and evaporated to yield 10.7 g (a yield of 87%) of as a brick red solid. Using various analytical procedures, this solid was determined to be 2-methyl-6-nitroquinoxaline.

5 2-Methyl-6-Aminoquinoxaline

A thick-walled Parr hydrogenation flask was charged with 2-methyl-6-nitroquinoxaline (10.0g, 52.9) and CH<sub>3</sub>OH (200 ml). The flask was flushed with a stream of nitrogen and 10% by weight palladium on charcoal (500 mg) was  
10 added. The flask was pressurized with hydrogen to 50 psi and maintained at this pressure for three (3) hours. The reaction mixture was filtered and washed through silicon dioxide and concentrated in vacuo to yield a tan solid. The crude material was chromatographed (SiO<sub>2</sub>; 95/5  
15 CHCl<sub>3</sub>/CH<sub>3</sub>OH saturated with NH<sub>3</sub> (g)) and recrystallized from benzene to yield 7.4 g (a yield of 88%) of a tan solid. Using various analytical procedures, this tan solid was determined to be 2-methyl-6-aminoquinoxaline.

2-Methyl-5-bromo-6-(2-imidazolin-2-ylamino) quinoxaline

20 By a series of reaction steps analogous to the reaction steps described above in Example 2 to produce 5-bromo-6-(2-imidazolin-2-ylamino) quinoxaline, the title compound (mp. 260° C) was prepared starting with 2-methyl-6-aminoquinoxaline in place of 6-aminoquinoxaline.

25 EXAMPLE 5

Preparation of 3-Methyl-5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline

3-Methyl-6-aminoquinoxaline

Pyruvic aldehyde (Aldrich, 892 mg, 4.95 mmol, 40%  
30 solution H<sub>2</sub>O) was added dropwise to a stirred solution of 1, 2, 4-triaminobenzene hydrochloride (1.0 g, 4.95 mmol) dissolved in 10% aqueous Na<sub>2</sub>CO<sub>3</sub> (15 ml). The mixture was heated at 100° C for two hours before cooling to room temperature. The mixture was extracted with CHCl<sub>3</sub>. The  
35 combined organic extracts were dried over MgSO<sub>4</sub> and

concentrated in vacuo to yield a brown solid. The crude product was chromatographed ( $\text{SiO}_2$ , 95/5  $\text{CHCl}_3/\text{CH}_3\text{OH}$  saturated with  $\text{NH}_3$  (g)) to yield 616 mg (a yield of 75%) of a yellow crystalline solid. An analytical sample was prepared by recrystallization from benzene, mp 170-173° C. Using various analytical procedures, the solid was determined to be 3-methyl-6-aminoquinoxaline.

3-Methyl-5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline

By a series of reaction steps analogous to the reaction steps described above in Example 2 to produce 5-bromo-6-(2 imidazolin-2-ylamino) quinoxaline, the title compound (mp > 260° C) was prepared starting with 3-methyl-6-aminoquinoxaline in place of 6-aminoquinoxaline.

EXAMPLE 6

Preparation of 2,3-dimethyl-5-bromo-6-(2-imidazolin-2-ylamino) quinoxaline.

2,3-Dimethyl-6-aminoquinoxaline

2,3-butanedione (7.03 g, 81.7 mmol) was added to a solution of 1,2,4-triaminobenzene hydrochloride (16.5 g, 81.7 mmol) in aqueous 10%  $\text{Na}_2\text{CO}_3$  (200 ml). The reaction mixture was stirred at room temperature for 15 minutes during which time a yellow precipitate formed. The reaction mixture was stirred for an additional 30 minutes before collecting the solid by vacuum filtration. The solid was washed with water, dried in vacuo and chromatographed ( $\text{SiO}_2$ , ethylacetate) to yield 11.7 g (86%) of a tan solid, mp 185-186°C. Using various analytical procedures, this solid was determined to be 2,3-dimethyl-6-aminoquinoxaline.

2,3-dimethyl-5-bromo-6-(2-imidazolin-2-ylamino)-quinoxaline

By a series of reaction steps analogous to the reaction steps described above in Example 2 to produce 5-bromo-6-(2-imidazolin-2-ylamino) quinoxaline, the title compound (mp 252-254°C) was prepared starting with 2,3-



dimethyl-6-aminoquinoxaline in place of 6-aminoquinoxaline.

#### EXAMPLE 7

The final quinoxaline derivative produced in Example 2, that is 5-bromo-6-(2-imidazolin-2-ylamino)quinoxaline, was tested for central nervous system anesthetization activity as follows.

Two (2) animal models were utilized to determine the central nervous system anesthetization activity of the quinoxaline derivative produced in Example 2.

The first of these animal models is identified generally as the mouse hexobarbital sleep time test. Briefly, the compound in question (in a dosage range of between 10 and 500 micrograms/kg, i.v.) and the barbiturate hexobarbital (75 mg/kg, i.p) are coadministered to mice weighing 20 to 22 grams. The hexobarbital produces sleep which lasts for 10 to 14 minutes. Compounds which have central nervous system anesthetization activity potentiate the sleep time induced by hexobarbital. Sleep time is assessed as the time associated with the loss of the animal's reflex to right itself when placed on its back. The  $ED_{15}$  is estimated from dose-response data as the effective dose which potentiates sleep time by 15 minutes. The second animal model used is identified generally as the rat activity test. Briefly, rats weighing 140 to 160 grams are placed into an environmentally isolated activity monitor five (5) minutes following administration of the compound in question (in the range of 1 to 1000 micrograms/kg, i.v.). Horizontal activity, measured in counts is determined for five (5) minutes. A dose-related loss of activity is obtained and fitted to an algorithm to estimate the  $ID_{50}$  which is the dose which decreases activity by 50%.

The final quinoxaline derivative produced in Example 2 was tested using both of the above-noted animal models.

For comparison purposes, clonidine and its hydrophilic analog, p-amino-clonidine, were also tested using these animal models.

Results of these tests are shown in the following table.

Compound	ED <sub>15</sub> (µg/kg) Mouse Sleep-Time	ID <sub>50</sub> (µg/kg) Rat Activity
Clonidine	75	26
p-Amino Clonidine	>500	302
10 Example 2	116	77

These data demonstrate that the quinoxaline derivative produced in Example 2 has substantial central nervous system anesthetization activity. In particular, the Example 2 compound has a similar degree of such activity as clonidine, which is known to exhibit significant anesthetization activity, and has substantially more of such activity than the hydrophilic analog of clonidine.

#### EXAMPLES 8 TO 13

The final quinoxaline derivative produced in each of Examples 1 to 6 is tested for activity as follows.

##### Rabbit Vas Deferens: Alpha 2 Adrenergic Receptors

New Zealand white rabbits (2-3 kg) are killed by CO<sub>2</sub> inhalation and the vasa deferentia is removed. The prostatic ends of the vasa deferentia (2-3 cm lengths) are mounted between platinum ring electrodes in 9 ml organ baths and bathed in Krebs bicarbonate solution of the following composition (millimolar): NaCl 118.0; KCl 4.7; CaCl<sub>2</sub> 2.5; MgSO<sub>4</sub> 1.2; KH<sub>2</sub> PO<sub>4</sub> 1.2; glucose 11.0; NaHCO<sub>3</sub> 25.0; which solution is maintained at 35° C and bubbled with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. The initial tension of the vas deferens is 0.5 g. The tissues are left to equilibrate for 30 minutes before stimulation is started. Vasa are then field stimulated (0.1 Hz, 2 ms pulse width at 90 mA) using a square wave stimulator (WPI A310 Accupulser with

A385 stimulus). The contractions of the tissue are recorded isometrically using Grass FT03 force-displacement transducers and displayed on a Grass Model 7D polygraph. A cumulative concentration-response relationship is obtained for the quinoxaline derivative being tested with a 4 minute contact time at each concentration. Each of the final quinoxaline derivatives of Examples 1 to 5 is effective to reduce the response height. Therefore, such compounds may be properly classified as Alpha 2 agonists since they are also inhibited pharmacologically by treatment with rauwolscine.

#### EXAMPLES 14 to 19

Each of the final quinoxaline derivatives produced in Examples 1 to 6 is tested for renal and blood pressure effects using the following method.

Young male (20-24 weeks old) Sprague-Dawley rats are used. Under ketamine (60 mg/kg b.wt. i.m.) and pentobarbital (i.p. to effect) anesthesia, medical grade plastic tubes are implanted into the abdominal aorta and vena cava via the femoral vessels. In addition, a Silastic-covered stainless steel cannula is sewn in the urinary bladder. After the surgery, the rats are housed individually and are allowed free access to food and water until the day of the experiment.

For about 7 to 10 days before surgery and during recovery, the rats are accustomed to a restraining cage by placement in the cage for 2 to 3 hours every 2nd and 3rd day. The cage is designed for renal clearance studies (a model G Restrainer sold by Braintree Scientific, Inc., Braintree, Massachusetts). The animals' adjustment to the cage is judged by the stability of blood pressure and heart rate.

For an experiment, a rat is placed in the restraining cage, and the arterial line is connected to a Statham pressure transducer and a Beckman Dynograph R61 to monitor

the mean arterial blood pressure, hereinafter referred to as MAP. The venous line is connected to an infusion pump system for infusion of replacement fluid. The quinoxaline derivative is administered intraduodenally by cannula.

5 The bladder cannula was extended with a silastic tube to facilitate collection of urine in preweighed tubes. The volume of urine is measured gravimetrically. Body weight is recorded before and after the experiment.

Throughout the experiments, 0.9% NaCl containing 10%  
10 polyfructosan (Inutest) and 1% sodium PAH is infused at a rate of 20 microliters/min. An equilibration period of 60 minutes is followed by two consecutive 30 minute control clearance periods. Then, the quinoxaline derivative is administered for 90 minutes. Urine collection is resumed  
15 10 minutes after the start of quinoxaline derivative administration. By this time the washout of the bladder cannula dead space (approximately 200 microliters) is completed. Three additional clearance measurements are made. Blood samples (150 microliters) are collected at  
20 the midpoint of urine collections. Plasma is separated and saved for analyses, and the cells are resuspended in saline and returned to the animals. Water and sodium loss is carefully replaced i.v. by a variable speed infusion pump.

25 Results of these tests indicate that the present quinoxaline derivatives produce renal effects, e.g., increased renal fluid flow. The effect on blood pressure of such derivatives is limited relative to such renal effects.

30 EXAMPLES 20 TO 25

Each of the final quinoxaline derivative produced in Examples 1 to 6 is tested for anti-diarrheal effects and blood pressure effects using the following method.

Cecectomies are performed in unfasted rats in a  
35 conventional manner. The cecectomized rats are put into

individual wire-bottomed cages placed over sheets of clean paper, and deprived of food and water for the duration of the assay. The MAP is monitored, as described in Examples 17 to 20, throughout the assay. Rats are given a 2 hour acclimatization period prior to the start of the assay in order to eliminate sporadic episodes of anxiety-induced defecation. During this period they are observed also for consistent occurrences of pelleted feces; an animal producing other than a pelleted stool is disqualified from the study.

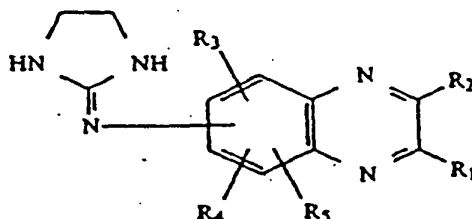
Diarrhea is induced with oral administration of 16,16-dimethyl prostaglandin E<sub>2</sub> (dmPGE<sub>2</sub>) in 3.5% EtOH. The quinoxaline derivative is administered by gavage after the onset of diarrheal episodes. The cage papers are removed and examined at 30 minute intervals for dmPGE<sub>2</sub>-induced diarrhea. Fecal output is recorded at each interval and fecal consistency is assigned a numerical score in each experimental group as follows: 1= normal pelleted stool; 2= soft-formed stools; 3= water stool and/or diarrhea. The fecal output index (FOI) is defined as the summation of the number of defecation episodes and their ranked consistency score within an observation period.

Results of these tests indicate that each of the final quinoxaline derivatives produced in Examples 1 to 5 provides substantial anti-diarrheal effects. Further, such anti-diarrheal effects are produced with relatively limited effects on blood pressure.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A method of treating a mammal comprising administering to a mammal an effective amount to provide a desired therapeutic effect in said mammal of a compound selected from the group consisting of those having the formula



10

, and pharmaceutically acceptable acid addition salts thereof and mixtures thereof, wherein  $R_1$  and  $R_2$  each is independently selected from the group consisting of H, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms, the 2-imidazolin-2-ylamino group may be in any of the 5-, 6-, 7- or 8-positions of the quinoxaline nucleus, and  $R_3$ ,  $R_4$  and  $R_5$  each is located in one of the remaining 5-, 6-, 7- or 8-positions of the quinoxaline nucleus and is independently selected from the group consisting of Cl, Br, H and alkyl radicals containing 1 to 3 carbon atoms, said desired therapeutic effect being selected from the group consisting of reduction in peripheral pain, anesthetization of the central nervous system, constriction of one or more blood vessels, reduction in or prevention of at least one effect of ischemia, decongestion of one or more nasal passages, reduction in at least one effect of an inflammatory disorder, increase in renal fluid flow, and alteration in the rate of fluid transport in the gastrointestinal tract.

2. The method of claim 1 wherein said desired therapeutic effect is a reduction in peripheral pain.

3. The method of claim 1 wherein said desired therapeutic effect is anesthetization of the central nervous system.

4. The method of claim 1 wherein said desired therapeutic effect is constriction of one or more blood vessels.

5. The method of claim 1 wherein said desired therapeutic effect is reduction in or prevention of at least one effect of ischemia.

6. The method of claim 1 wherein said therapeutic effect is decongestion of one or more nasal passages.

7. The method of claim 1 wherein said desired therapeutic effect is reduction in at least one effect of an inflammatory disorder.

8. The method of claim 1 wherein said desired therapeutic effect is increase in renal fluid flow.

9. The method of claim 1 wherein said desired therapeutic effect is alteration in the rate of fluid transport in the gastrointestinal tract.

10. The method of claim 1 wherein the 2-imidazolin-2-ylamino group is in the 6- position of the quinoxaline nucleus,  $R_3$  is in the 5- position of the quinoxaline nucleus and is selected from the group consisting of Cl, Br and alkyl radicals containing 1 to 3 atoms, and  $R_4$  and  $R_5$  are both H.

11. The method of claim 1 wherein  $R_2$  is a methyl radical.

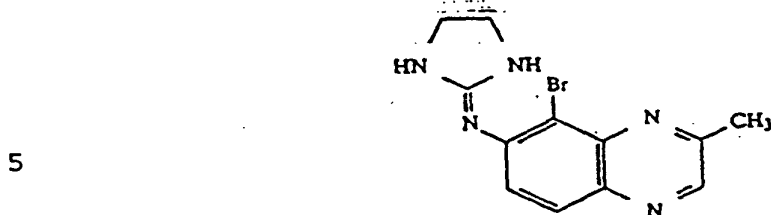
12. The method of claim 1 wherein  $R_1$  is H and  $R_2$  is selected from the group consisting of alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms.

13. The method of claim 10 wherein  $R_2$  is a methyl radical.

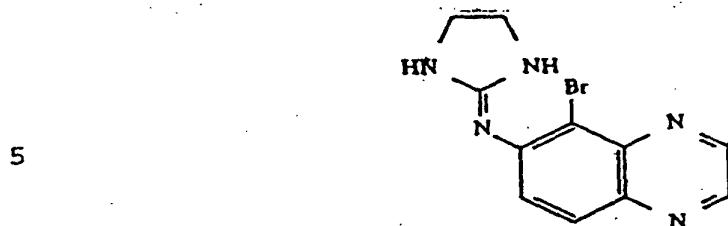
14. The method of claim 10 wherein  $R_3$  is Br.

15. The method of claim 13 wherein  $R_3$  is Br.

16. The method of claim 1 wherein said formula is:



17. The method of claim 1 wherein said formula is



18. The method of claim 1 wherein  $R_3$  is in the 5-position of the quinoxaline nucleus and is selected from the group consisting of H and alkyl radicals containing 1 to 3 carbon atoms

19. The method of claim 18 wherein the 2-imidazolin-2-ylamino group is in the 6-position of the quinoxaline nucleus, and  $R_4$  and  $R_5$  are both H.

20. The method of claim 18 wherein both  $R_1$  and  $R_2$



are H.

21. The method of claim 18 wherein both  $R_1$  and  $R_2$  are H.

5

22. The method of claim 18 wherein  $R_3$  is selected from the group consisting of H and methyl radical.

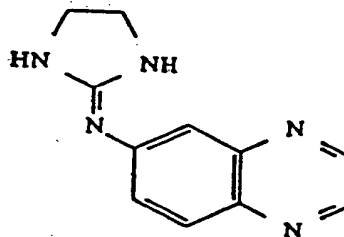
23. The method of claim 19 wherein  $R_3$  is selected from the group consisting of H and methyl radical.

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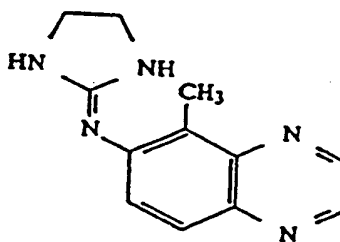
24. The method of claim 21 wherein  $R_3$  is selected from the group consisting of H and methyl radical.

25. The method of claim 18 wherein said formula is:

5



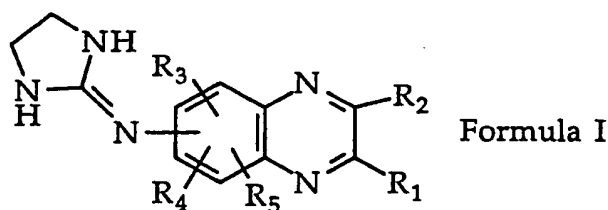
26. The method of claim 17 wherein said formula is:



## AMENDED CLAIMS

[received by the International Bureau on 06 March 1995 (06.03.95);  
original claims 14 and 17 cancelled; original claims 1-13, 15, 16  
and 18-26 amended. (4 pages)]

- 5           1. The use of a compound of formula I, including pharmaceutically acceptable salts thereof and mixtures thereof,



- 10   for the manufacture of a medicament for providing a mammal with a desired therapeutic effect wherein R<sub>1</sub> and R<sub>2</sub> each is independently selected from the group consisting of H, alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms, the 2-imidazolin-2-ylamino group may be in any of the 5-, 6-, 7- or 8- positions of the quinoxaline nucleus, and R<sub>3</sub>, R<sub>4</sub>  
15   and R<sub>5</sub> each is located in one of the remaining 5-, 6-, 7- or 8- positions of the quinoxaline nucleus and is independently selected from the group consisting of Cl, Br, H and alkyl radicals containing 1 to 3 carbon atoms except that when Br is at position 5 and the 2-imidazolin-2-ylamino group is at position 6 of the quinoxaline ring and positions 7 and 8 are hydrogen then at least one of R<sub>1</sub> and  
20   R<sub>2</sub> is not hydrogen, said desired therapeutic effect being selected from the group consisting of reduction in peripheral pain, anesthetization of the central nervous system, constriction of one or more blood vessels, reduction in or prevention of at least one effect of ischemia, decongestion of one or more nasal passages, reduction in at least one effect of an inflammatory disorder, increase  
25   in renal fluid flow, and alteration in the rate of fluid transport in the gastrointestinal tract.

2. The use of claim 1 wherein said desired therapeutic effect is a reduction in peripheral pain.

30

3. The use of claim 1 wherein said desired therapeutic effect is anesthetization of the central nervous system.
- 5 4. The use of claim 1 wherein said desired therapeutic effect is constriction of one or more blood vessels.
5. The use of claim 1 wherein said desired therapeutic effect is reduction in or prevention of at least one effect of ischemia.
- 10 6. The use of claim 1 wherein said desired therapeutic effect is decongestion of one or more nasal passages.
7. The use of claim 1 wherein said desired therapeutic effect is reduction in at  
15 least one effect of an inflammatory disorder.
8. The use of claim 1 wherein said desired therapeutic effect is increase in renal fluid flow.
- 20 9. The use of claim 1 wherein said desired therapeutic effect is alteration in the rate of fluid transport in the gastrointestinal tract.
10. The use of claim 1 wherein the 2-imidazolin-2-ylamino group is in the 6-position of the quinoxaline ring, R<sub>3</sub> is in the 5-position of the quinoxaline ring  
25 and is selected from the group consisting of Cl and alkyl radicals of 1 to 3 carbon atoms and R<sub>4</sub> and R<sub>5</sub> are both hydrogen.
11. The use of claim 1 wherein R<sub>2</sub> is a methyl radical.

12. The use of claim 1 wherein  $R_1$  is H and  $R_2$  is selected from the group consisting of alkyl radicals containing 1 to 4 carbon atoms and alkoxy radicals containing 1 to 4 carbon atoms.

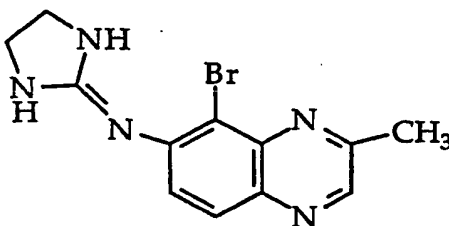
5

13. The use of claim 10 wherein  $R_2$  is a methyl radical.

14. (Deleted).

10 15. The use of claim 13 wherein  $R_3$  is Br.

16. The use of claim 12 wherein said formula 1 is:



15 17. (Deleted).

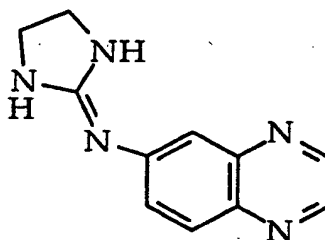
18. The use of claim 1 wherein  $R_3$  is in the 5-position of the quinoxaline ring and is selected from the group consisting of H and alkyl radicals containing 1 to 3 carbon atoms.

20

19. The use of claim 18 wherein the 2-imidazolin-2-ylamino group is in the 6-position of the quinoxaline ring and  $R_4$  and  $R_5$  are both H.

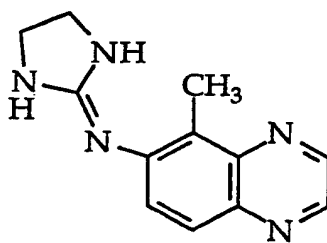
20. The use of claim 18 wherein both  $R_1$  and  $R_2$  are H.

21. The use of claim 19 wherein both  $R_1$  and  $R_2$  are H.
22. The use of claim 18 wherein  $R_3$  is selected from the group consisting of H  
5 and methyl radical.
23. The use of claim 19 wherein  $R_3$  is selected from the group consisting of H  
and methyl radical.
- 10 24. The use of claim 21 wherein  $R_3$  is selected from the group consisting of H  
and methyl radical.
25. The use of claim 18 wherein said formula 1 is:



15

26. The use of claim 17 wherein said formula is:



**STATEMENT UNDER ARTICLE 19**

The amendments presented to the International Bureau under Article 19 are intended to remove the compound disclosed in the prior art cited in the ISR from the scope of the claims. The referenced compound with the test number UK 14,304 and named 5-bromo-6-(2-imidazolin-2-yl-amino)quinoxaline has been provisoed or deleted out of the scope of the amended claims.

Additionally, the method of use claims (all of the claims of the present invention have been amended to claims to a method of manufacture of a medicament, in response to the objection raised in the ISA.

## INTERNATIONAL SEARCH REPORT

Intern. Application No.

PCT/US 94/10569

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 422 878 (ALLERGAN, INC.) 17 April 1991 see the whole document ---	1,8-26
X	WO,A,93 13771 (ALLERGAN, INC.) 22 July 1993 see the whole document ---	1-7, 10-26
X	BR J PHARMACOL (ENGLAND), JUN 1986, VOL. 88, NO. 2, PAGE(S) 345-54, Berridge TL et al 'Characterization of alpha-adrenoceptors in the vasculature of the canine nasal mucosa.' see the whole document --- -/--	1,6, 10-26



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

20 December 1994

Date of mailing of the international search report

06.01.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+ 31-70) 340-3016

Authorized officer

Stierman, B

## INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/US 94/10569

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J AUTON PHARMACOL (ENGLAND), APR 1993, VOL. 13, NO. 2, PAGE(S) 115-26, Thaina P et al 'Inhibition by alpha 2-adrenoceptor agonists of contractions of rabbit isolated colon elicited by pelvic nerve stimulation.' see the whole document ---	1,9-26
X	NEUROPHARMACOLOGY, 1986, VOL. 25, PAGE(S) 391-6 Hayes, A. G. et al 'Alpha-adrenoceptor-mediated antinociception and sedation in the rat and dog' see the whole document ---	1-3, 10-26
X	DRUG DEV. RES., 1986, VOL. 7, PAGE(S) 209-20 Colpaert, Francis C. 'Maximal magnitude of effect and potency of putative.alpha.-adrenoceptor agonists in causing CNS depression, in relaxing muscle, and in lowering body temperature in rat' see the whole document ---	1,3, 10-26
X	GASTROENTEROLOGY, 1984, VOL. 86, PAGE(S) 120-8 Dharmasathaphorn, Kiertisin et al 'Effects of structure-activity relationships of.alpha.-adrenergic compounds on electrolyte transport in the rabbit ileum and rat colon' see the whole document ---	1,9-26
X	US,A,4 188 393 (P. NEUMANN) 12 February 1980 see the whole document ---	1,7, 10-26
A	DE,A,23 09 160 (PFIZER CORP.) 27 September 1973 see the whole document & US,A,3 890 319 cited in the application ---	1-26
A	EP,A,0 426 390 (ALLERGAN, INC.) -8 May 1991 see the whole document & US,A,5 021 416 cited in the application -----	1-26



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/ 10569

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-26  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claims 1 to 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-15, 18-24  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
In view of the large number of compounds which are theoretically defined by the general formula of claim 1, the search had to be restricted to the compounds explicitly mentioned in the claims and to the general inventive concept.
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

information on patent family members

Intern. Application No

PCT/US 94/10569

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		SE-B- 417204	02-03-81

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/US 94/10569

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		JP-A- 3153626	01-07-91
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		AU-A- 6396690	09-05-91
		CA-A- 2025189	01-05-91
		EP-A- 0426390	08-05-91
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